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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/761,202	01/22/2004	Guping Tang	4249-0115P	2330

2292 7590 12/01/2008
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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
12/01/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/761,202	TANG ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-19 and 21-35* is/are pending in the application.

4a) Of the above claim(s) *30-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-19 and 21-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office action.

2. Claims 3, 4, 20, and 36-39 have been cancelled. Claims 30-35 have been withdrawn.

Claims 1, 2, 5-19, and 21-29 are under examination.

Response to Arguments

Claim Objections

3. The objection to claims 1 and 16 is withdrawn in response to Applicant's argument filed on 08/15/2008. In the telephone conversation which took place on 7/14/2008, Applicant's representative pointed out that, although in the reply filed on 10/5/2007 the claims have been amended to consistently spell the term "polyethylenimine", the amendments were not entered despite the filing of an RCE on 12/5/2007 requesting such entry. The Office regrets any inconvenience this may have caused the Applicant. The amendments to the claims filed on 10/5/2007 are hereby entered.

Claim Rejections - 35 USC § 103

4. The rejection of claims 1, 2, 5-19, and 21-29 under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (WO 00/33885), in view of each Gosselin et al. (Bioconjugate Chem, 2001, 12: 989-994), Cheng et al. (U.S. Patent No. 7,270,808), and Wachter et al. (Nucleic Acids Research, 1986, 14: 7985-7994) is withdrawn in response to Applicant's arguments filed on 08/15/2008. Specifically, the argument that Gosselin et al. do not teach linear PEI was found persuasive. It is noted that all PEI could be linear or branched and that, although Gosselin et al. teach PEI with molecular weight of 800 Da, they do not specify that their PEI is linear.

New Rejections

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 2, 5-19, and 21-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (WO 00/33885, of record), in view of each Kosak et al. (PGPUB 2001/0034333, of record), Cheng et al. (U.S. Patent No. 7,270,808, of record), and Wachter et al. (Nucleic Acids Research, 1986, 14: 7985-7994, of record).

Davis et al. teach a biodegradable, linear cyclodextrin block copolymer and a method of synthesizing the block copolymer by modifying β-cyclodextrin at only two positions and reacting the modified cyclodextrin with a linear polycationic co-monomer

(such as spermine) to form a block copolymer wherein cyclodextrin is attached to the polycation and not to another cyclodextrin moiety; since it contains a polycation, the polymer has a net positive charge and is therefore capable of complexing with nucleic acids (claims 1, 2, 8, 16, 17, and 29) (p. 8, lines 9-30, p. 9, lines 1-12 and 24-29, p. 12, lines 12-30, p. 13, lines 5-11, p. 15, p. 16, line 2). Davis et al. teach their copolymer as being suitable for nucleic acid delivery to a cell (claim 1) (p. 1, lines 5 and 6, p. 29, lines 12-16).

Although Davis et al. teach a polycation, they do not specifically teach a cyclodextrin block copolymer wherein the co-monomer is low molecular weight PEI (claims 1, 5-6, 16, 21-23, and 29). However, at the time the invention was made, the use of low molecular PEI to obtain PEI-cyclodextrin copolymers suitable for nucleic acid delivery was taught by the prior art. For example, Kosak et al. teach obtaining an amphiphilic PEI-cyclodextrin copolymer by attaching 800 Da PEI, wherein the amphiphilic copolymer is able to efficiently condense nucleic acids (i.e., PEI with molecular weight of less than 10,000 Da) to cyclodextrin dimmers, trimers, or polymers (p. 24, paragraphs 0378 and 0379, p. 25, paragraph 0380). Based on these teachings, one of skill in the art would have known that 800 Da PEI could be successfully used to obtain cyclodextrin copolymers for nucleic acid delivery. It would have been obvious to one of skill in the art, at the time the invention was made, to modify the copolymer of Davis et al. by replacing their linear polycation with a linear 800 Da PEI to achieve the predictable result of obtaining a linear cyclodextrin block copolymer suitable for delivering nucleic acids to cells.

Davis et al. and Kosak et al. do not teach cross-linking cyclodextrin and PEI via an ester bond (claims 11, 12, 24, and 25). However, at the time of filing the use of biodegradable ester bonds to couple cyclodextrin to PEI was known in the prior art (see Cheng et al., column 10, lines 26-30, column 24, lines 3-5). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Davis et al. and Kosak et al. by using the teachings of Cheng et al. to link the cyclodextrin and the linear PEI of Davis et al. and Kosak et al. to achieve the predictable result of obtaining a biodegradable cyclodextrin-PEI block copolymer.

With respect to the limitation of using 1,1 '-carbonyldiimidazole as an activating agent (claims 9, 10, 18, and 19), it is noted that the art teaches that that 1.1'-carbonyldiimidazzole can be successfully used to link hydroxyl and amine groups (i.e., groups found on cyclodextrin and PEI, respectively) (see Cheng et al., column 61, lines 49-55; Wachter et al., Abstract, p. 7895, p. 7989, Fig. 1). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to use 1.1'-carbonyldiimidazzole to achieve the predictable result of coupling cyclodextrin to PEI.

With respect to the limitations recited in claims 13-15 and 26-28, absent evidence of unexpected results, it would have been obvious to one of skill in the art to vary the parameters (i.e., the number of PEI units within the copolymer) with the purpose of optimizing the results (i.e., nucleic uptake by cells). Again, absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation (see MPEP 2144.05 [R-5]).

Applicant's arguments are answered below to the extent that they pertain to the instant rejection.

Applicant traversed the instant rejection on the grounds that the present invention shows unexpected efficacy *in vivo* experiments. Compared with Davis, gene delivery efficiency of PEI is superior to that of spermine. For example, Applicants show that the polymer of the invention is capable of *in vivo* delivery (see the specification p. 12, lines 11-21); in contrast, there is no published data on in vivo gene delivery by spermine.

With respect to Cheng et al., Applicant argues that they teach branched polymers and that this is evident merely from examination of formulae (I), (II) and (III) of the reference. Thus, Applicant argues, Cheng et al. teach away from the present invention, which due to the features described in claim 1 is a linear polymer. Furthermore, formula (III) of Cheng et al. shows a central CyD molecule having four "linker" groups; this embodiment includes linkages in excess of two to the CyD molecule, as recited in the present claims. Thus, Applicant argues, one of skill would not combine Davis with either Gosselin or Cheng with any expectation of success in making the presently claimed invention.

With respect to Wachter et al., Applicant argues that, although the Examiner asserts that 1,1 '-carbonyldiimidazole can be successfully used to link hydroxyl and amine groups, claims 9, 10, 18, and 19 incorporate claims 1 and 16, wherein each cyclodextrin moiety is attached to one or two PEI moieties and not to any other cyclodextrin moiety and that the PEI is less than 10 kDa molecular weight. Applicant

argues that Wachter does not address the failure of Davis and Gosselin to suggest these features of the invention. Furthermore, Applicant argues, Wachter describes linking of carbonyldiimidazole nucleic acid to biotin through hexamethylene diamine. There is no suggestion whatsoever by Wachter that the carbonyldiimidazole reagent is suitable for forming a linear co-polymer of cyclodextrin with a polyethylenimine, i.e., that two large polymeric molecules could be effectively joined to form a linear, alternating co-polymer.

Applicant's arguments are acknowledged however, the rejection is maintained for the following reasons:

With respect to the argument that, compared with Davis, gene delivery efficiency of PEI is superior to that of spermine, it is noted that the instant rejection is based on a combination of references, which combination teaches PEI and not spermine. Moreover, PEI was known in the prior art as being a very efficient agent for both *in vitro* and *in vivo* gene delivery (see Kircheis et al., Advanced Drug Delivery Reviews, 2001, 53: 341-358, Abstract, p. 342, column 2, first paragraph, p. 346, column 2, last paragraph, p. 347, columns 1 and 2). Therefore, Applicant's argument that the present invention shows unexpected efficacy *in vivo* experiments is not found persuasive. Applicant's argument, by teaching branched polymers, Cheng et al. teach away from the present invention is not found persuasive. The instant rejection is based on modifying the linear copolymer of Davis et al. to obtain a linear copolymer comprising PEI and cyclodextrin, wherein the PEI and cyclodextrin are linked via ester bonds. Cheng et al. was only cited for providing evidence that PEI and cyclodextrin can be

coupled via ester bonds. MPEP clearly states that a teaching away from the invention is a teaching which renders prior art unsatisfactory for the intended purpose (MPEP 2145 [R-6] X D); there is no teaching in Cheng et al. that linking cyclodextrin with linear PEI to obtain a linear block copolymer would lead to unsatisfactory results. With respect to Wachter et al., Applicant argues that the reference describes the linking of carbonyldiimidazole nucleic acid to biotin through hexamethylene diamine and that there is no suggestion of carbonyldiimidazole as being suitable for forming a linear copolymer of cyclodextrin with a polyethylenimine. Such is just an argument which is not supported by any evidence and therefore, it is not found persuasive. Carbonyldiimidazole is widely used to couple hydroxyl-containing compounds and amino-containing compounds, wherein carbonyldiimidazole activate the hydroxyl groups rendering them capable of reacting with the amino groups. One of skill in the art would know that carbonyldiimidazole could be used to couple any hydroxyl-containing compound with any amino-containing compound. Beside an argument, Applicant did not provide any evidence to prove that cyclodextrin and PEI cannot be coupled via carbonyldiimidazole.

Conclusion

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Kircheis et al. (Advanced Drug Delivery Reviews, 2001, 53: 341-358) was cited in response to Applicant's argument that the use of PEI result in

unexpected efficiency. Specifically, the referenced teaches that the high efficiency of PEI as a delivery agent was known in the art before the claimed invention was made.

8. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/

Examiner, Art Unit 1633